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Absolute Configuration of 3-Quinuclidinyl Benzilate and the Behavioral Effect in the Dog of the Optical Isomers

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Usually, a great difference in potency is found between optical isomers of anticholinergic esters with asymmetric centers in the acid moiety.[1,2] But when the asymmetric center is situated in the alcoholic part of the ester, this effect is not always noted. Hence, five anticholinergic esters derived from the isomers of β-methylcholine showed *R/S* potency ratios close to one.[2] However, Sternbach and Kaiser[3,4] found a marked difference in antispasmodic action on isolated rabbit intestine between the enantiomers of quinuclidinyl diphenylacetate, although no difference was found between the two isomers of quaternized quinuclidinyl benzilate.

In the cases where small or no differences have been found between the pharmacological effects of the isomers, quaternized drugs have always been used. The esters of quinuclidine appear to be exceptions to the findings which state that quaternization increases the activity of these types of drugs.[5] Hence, it was of interest to study the pharmacological effects of the enantiomers of 3-quinuclidinyl benzilate (QB) as a base. Moreover QB is a very potent drug, particularly as a central agent,[6] and because of the rigid structure of quinuclidine this compound might show a higher degree of stereospecificity than the esters of β-methylcholine.

In the present study the (+) and (−) enantiomers of 3-quinuclidinyl benzilate were isolated and their absolute configurations determined by the use of the X-ray anomalous dispersion technique.[7] In addition, a pharmacological test was performed on the enantiomers.

Experimental Section†

Resolution of (±)-3-quinuclidinol was performed according to Sternbach and Kaiser[3] using (+)-camphor-10-sulfonic acid. While this manuscript was being prepared, a method of isolating (+)-3-quinuclidinol in the pure state was published.[8] All experimental data are listed in Table I.

(−)-3-Quinuclidinyl benzilate was prepared from equivalent amounts of methyl benzilate and (−)-3-quinuclidinol in the presence of sodium hydride,[9,‡] yield 79%. After three recrystallizations from acetone, the product showed less than 0.1% of impurities according to glc (on 5% OV 210 column).

Crystals of (−)-3-quinuclidinyl benzilate hydrobromide were prepared from the base and hydrobromic acid solved in methanol and recrystallized from acetone–methanol with slow evaporation and cooling. After one week, crystals large enough for single crystal X-ray diffraction analysis were obtained, $[\alpha]^{22}D - 26.2°$ (*c* 0.6, 0.2 *M* HCl), which corresponds to $[\alpha]^{22}D - 32.5°$ for the free base.

(+)-3-Quinuclidinyl Benzilate. (+)-3-Quinuclidinol, partially resolved, was converted to the corresponding ester using the same method as described for the (−) isomer, yield 59%. The product was purified by fractional crystallizations from acetone–methanol, 30:1, the first fraction being richest in the (+) isomer. Five recrystallizations yielded a product with $[\alpha]^{22}D + 32.6°$. It was not possible to obtain higher optical purity for the last product by further recrystallizations from this solvent mixture. The glc analysis (on 5% OV 1 column) showed small amounts of methyl benzilate and benzophenone (together less than 1%).

Determination of the Absolute Configuration. The structure factors for the *R* configuration of QB hydrobromide were calculated with the positional atomic coordinates and temperature factors from the crystal structure determination.[10] The atomic scattering factors for Cu Kα radiation with corrections for the anomalous scattering of the bromine ions were taken from the International Tables.[11] The calculations were performed on an IBM 360/75 computer with the program system of Bergin.[12] From these data 20 Bijvoet pairs, which showed the effect of anomalous scattering most significantly, were selected in the *hk*1–*hk*3 layers. The observed intensities were obtained from a single crystal of (−)-quinuclidinyl benzilate hydrobromide. The crystal was trimmed to a sphere (radius 0.23 mm) in order to avoid differences in absorption for the two reflections of each Bijvoet pair. The reflections were recorded in an integrating Weissenberg camera with Ni-filtered Cu Kα radiation and multiple film technique. The intensities of the 20 pairs selected from the structure factor calculations were derived from microdensitometer data. Due corrections for background and film factors were made. The calculated structure factors were converted to I_{calcd} and scaled to I_{obsd}.

Pharmacological Tests. Behavioral and peripheral effects of the synthetized isomers have been studied in adult beagles according to a method described by Albanus.[6] Centrally active anticholinergic drugs elicit a typical behavioral syndrome in dogs called the central anticholinergic syndrome (CAS). This is manifested by symptoms such as ataxia and decreased environmental awareness, the latter being manifested as nonretreating behavior. The threshold dose to elicit these two symptoms is used as the index of central anticholinergic potency. In addition salivation and heart rate were recorded. Aqueous solutions of the enantiomers of QB were prepared in concentrations of 0.1–10 mg/ml. The solutions were equimolar with respect to hydrochloric acid and contained 10% methanol because of the low water solubility of the drugs. The injections were made subcutaneously with 0.1 ml/kg body weight. The threshold dose to elicit the CAS for the most inactive isomer was determined.

Results and Discussion

The observed Bijvoet pairs exhibited differences§ which agreed well with the calculated values based upon an *R* configuration. This shows unequivocally that (−)-QB hydrobromide possesses the *R* configuration. Belleau and Pauling[13] have determined the absolute configuration of (−)-quinuclidinol to be *R*. This indicates that no inversion occurred during the transesterification of methyl benzilate with 3-quinuclidinol.

The spatial arrangement of atoms for the *R* configuration of QB in crystals of the hydrobromide is illustrated in the perspective drawing of Figure 1. The ether oxygen atom is

†Melting points (uncorrected) were determined on a Leitz melting point microscope. Optical rotation measurements were carried out on a Perkin-Elmer 141 polarimeter and nmr spectra on a Varian A 60A spectrophotometer. Glc analyses were performed by I. Lindgren and elemental analyses were carried out by C. Lamrell both at this laboratory.

‡G. Wallerberg, *et al.*, unpublished work from this laboratory, 1970.

§Observed and calculated intensities for 40 reflections are on file in the offices of the ACS.

Table I. Specific Rotation and Melting Points for the Compounds Studied

Compound	Isomer	$[\alpha]^{22}D$, deg	c	Medium	Mp, °C	Lit.[3] $[\alpha]^{25}D$, deg	Lit.[3] c	Lit.[3] Medium
Quinuclidinol	(−)	−1.8	5	H_2O		−0.3	7	H_2O
(+)-camphorsulfonate	(+)	+20.2[a]	3	H_2O		+20.0[a]	7	H_2O
Quinuclidinol	(−)	−44.7	3	1 *M* HCl		−43.8	3	1 *M* HCl
	(+)	+16.0[a]	3	1 *M* HCl				
Quinuclidinyl benzilate	(−)	−33.8	0.5	0.2 *M* HCl	189–190			
	(+)	+32.6	0.5	0.2 *M* HCl	188–190			
	(±)				166–168			

[a]Partially resolved.

Table II. Pharmacological Effects for Different Doses of the Isomers of 3-Quinuclidinyl Benzilate

Isomer	Dose, mg/kg	Ataxia	Nonretreating	Salivation and heart rate	Number of experiments
Racemate	0.01	+	+	+	2 (lit.[6])
Levo	0.01	+	+	+	3
Dextro	0.01	−	−	−	1
Dextro	0.05	−	−	−	1
Dextro	0.1	−	−	−	1
Dextro	0.2[a]	+	2+/1−[b]	1+/2−[c]	3
Dextro	0.3	+	+	−	2
Dextro	0.5	+	+	−	1
Dextro	1.0	+	+	+	1

[a]Estimated threshold dose for central effects. [b]Two out of three animals gave a positive effect. [c]One out of three animals gave a positive effect.

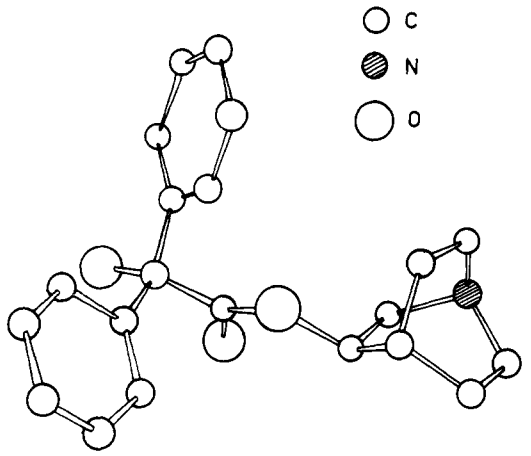

Figure 1. A perspective drawing of the (*R*)-(−)-3-quinuclidinyl benzilate molecule as it is found in crystals of the hydrobromide.

situated anticlinal to the nitrogen atom, the torsion angle being +125° between the plane O–C–C and the plane C–C–N.

The results of the pharmacological tests are illustrated in Table II. It can be concluded that the levoratory QB is at least 20 times more potent than its (+) isomer. The test method is not accurate enough to distinguish between the potency of the (−) isomer and the racemate. Since the maximum impurity of the (−) isomer in the (+) isomer is 1.8% calculated from the optical rotation measurements, the effect of the (+) isomer might be attributable to the impurity. Thus it is not possible to say that the compound with the *S* configuration lacks activity. However, the results agree well with those of Sternbach and Kaiser[3,4] with respect to the fact that the nonquaternized drugs show a difference in potency between the enantiomers derived from asymmetric alcohols, while the quaternized drugs do not. This behavior might then be unique for esters of quinuclidine.

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Terpene Compounds as Drugs. 11. Anabolic 19-Nortestosterone Terpenoates

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As part of our program in the field of terpene compounds as drugs,[1,2] we have prepared for preliminary anabolic testing[3] a number of esters of 19-nortestosterone with acyclic and cyclic terpenyl acids. The new substances (Table I) were obtained by allowing the steroid alcohol to